

**ATCC Deposit No.: Unassigned****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

**ATCC Deposit No.: Unassigned****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

**SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

**NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

What is claimed:

1. An albumin fusion protein comprising a Therapeutic protein:X and albumin comprising the amino acid sequence of SEQ ID NO:18.
- 5 2. An albumin fusion protein comprising a Therapeutic protein:X and a fragment or a variant of the amino acid sequence of SEQ ID NO:18, wherein said fragment or variant has albumin activity.
- 10 3. The albumin fusion protein of claim 2, wherein said albumin activity is the ability to prolong the shelf life of the Therapeutic protein:X compared to the shelf-life of the Therapeutic protein:X in an unfused state.
- 15 4. The albumin fusion protein of claim 2, wherein the fragment or variant comprises the amino acid sequence of amino acids 1-387 of SEQ ID NO:18.
5. The albumin fusion protein of any one of claims 1-4, wherein said Therapeutic protein:X comprises IL-2.
- 20 6. An albumin fusion protein comprising a fragment or variant of a Therapeutic protein:X, and albumin comprising the amino acid sequence of SEQ ID NO:18, wherein said fragment or variant has a biological activity of the Therapeutic protein:X.
- 25 7. The albumin fusion protein of claim 6, wherein said Therapeutic protein:X comprises IL-2, and wherein said fragment or variant has T cell proliferative activity or T cell activation activity.
8. The albumin fusion protein of any one of claims 1-4 or 6, wherein said Therapeutic protein:X, or fragment or variant thereof, comprises a protein selected from the

group consisting of:

- (a) calcitonin;
- (b) growth hormone releasing factor;
- (c) IL-2 fusion protein;
- 5 (d) insulin-like growth factor-1;
- (e) interferon beta; and
- (f) parathyroid hormone.

9. The albumin fusion protein of any one of claims 1-8, wherein the  
10 Therapeutic protein:X, or fragment or variant thereof, is fused to the N-terminus of albumin,  
or the N-terminus of the fragment or variant of albumin.

10. The albumin fusion protein of any one of claims 1-8, wherein the  
Therapeutic protein:X, or fragment or variant thereof, is fused to the C-terminus of albumin,  
15 or the C-terminus of the fragment or variant of albumin.

11. The albumin fusion protein of any one of claims 1-8, wherein the  
Therapeutic protein:X, or fragment or variant thereof, is fused to the N- terminus and C-  
terminus of albumin, or the N-terminus and the C-terminus of the fragment or variant of  
20 albumin.

12. The albumin fusion protein of any one of claims 1-8, which comprises a first  
Therapeutic protein:X, or fragment or variant thereof, and a second Therapeutic protein:X,  
or fragment or variant thereof, wherein said first Therapeutic protein:X, or fragment or  
25 variant thereof, is different from said second Therapeutic protein:X, or fragment or variant  
thereof.

13. The albumin fusion protein of any one of claims 1-11, wherein the

Therapeutic protein:X, or fragment or variant thereof, is separated from the albumin or the fragment or variant of albumin by a linker.

14. The albumin fusion protein of any one of claims 1-11, wherein the albumin  
5 fusion protein has the following formula:

R1-L-R2; R2-L-R1; or R1-L-R2-L-R1,

wherein R1 is Therapeutic protein:X, or fragment or variant thereof, L is a peptide linker, and R2 is albumin comprising the amino acid sequence of SEQ ID NO:18 or fragment or variant of albumin.

10

15. The albumin fusion protein of any one of claims 1-14, wherein the shelf-life of the albumin fusion protein is greater than the shelf-life of the Therapeutic protein:X, or fragment or variant thereof, in an unfused state.

15

16. The albumin fusion protein of any one of claims 1-14, wherein the in vitro biological activity of the Therapeutic protein:X, or fragment or variant thereof, fused to albumin, or fragment or variant thereof, is greater than the in vitro biological activity of the Therapeutic protein:X, or fragment or variant thereof, in an unfused state.

20

17. The albumin fusion protein of any one of claims 1-14, wherein the in vivo biological activity of the Therapeutic protein:X, or fragment or variant thereof, fused to albumin, or fragment or variant thereof, is greater than the in vivo biological activity of the Therapeutic protein:X, or fragment or variant thereof, in an unfused state.

25

18. An albumin fusion protein comprising a Therapeutic protein:X, or fragment or variant thereof, inserted into an albumin comprising the amino acid sequence of SEQ ID NO:18 or fragment or variant thereof.

19. An albumin fusion protein comprising a Therapeutic protein:X, or fragment or variant thereof, inserted into an albumin comprising an amino acid sequence selected from the group consisting of:

- (a) amino acids 54 to 61 of SEQ ID NO:18;
- 5 (b) amino acids 76 to 89 of SEQ ID NO:18;
- (c) amino acids 92 to 100 of SEQ ID NO:18;
- (d) amino acids 170 to 176 of SEQ ID NO:18;
- (e) amino acids 247 to 252 of SEQ ID NO:18;
- (f) amino acids 266 to 277 of SEQ ID NO:18;
- 10 (g) amino acids 280 to 288 of SEQ ID NO:18;
- (h) amino acids 362 to 368 of SEQ ID NO:18;
- (i) amino acids 439 to 447 of SEQ ID NO:18;
- (j) amino acids 462 to 475 of SEQ ID NO:18;
- (k) amino acids 478 to 486 of SEQ ID NO:18; and
- 15 (l) amino acids 560 to 566 of SEQ ID NO:18.

20. The albumin fusion protein of claims 18 or 19, wherein said albumin fusion protein comprises a portion of albumin sufficient to prolong the shelf-life of the Therapeutic protein:X, or fragment or variant thereof, as compared to the shelf-life of the Therapeutic protein:X, or fragment or variant thereof, in an unfused state.

21. The albumin fusion protein of claims 18 or 19, wherein said albumin fusion protein comprises a portion of albumin sufficient to prolong the in vitro biological activity of the Therapeutic protein:X, or fragment or variant thereof, fused to albumin as compared to the in vitro biological activity of the Therapeutic protein:X, or fragment or variant thereof, in an unfused state.

22. The albumin fusion protein of claims 18 or 19 wherein said albumin fusion

protein comprises a portion of albumin sufficient to prolong the in vivo biological activity of the Therapeutic protein:X, or fragment or variant thereof, fused to albumin compared to the in vivo biological activity of the Therapeutic protein:X, or fragment or variant thereof, in an unfused state.

5

23. The albumin fusion protein of any one of claims 1-22, which is non-glycosylated.

10 24. The albumin fusion protein of any one of claims 1-22, which is expressed in yeast.

15 25. The albumin fusion protein of claim 24, wherein the yeast is glycosylation deficient.

20 26. The albumin fusion protein of claim 24 wherein the yeast is glycosylation and protease deficient.

27. The albumin fusion protein of any one of claims 1-22, which is expressed by a mammalian cell.

28. The albumin fusion protein of any one of claims 1-22, wherein the albumin fusion protein is expressed by a mammalian cell in culture.

29. The albumin fusion protein of any one of claims 1-22, wherein the albumin 25 fusion protein further comprises a secretion leader sequence.

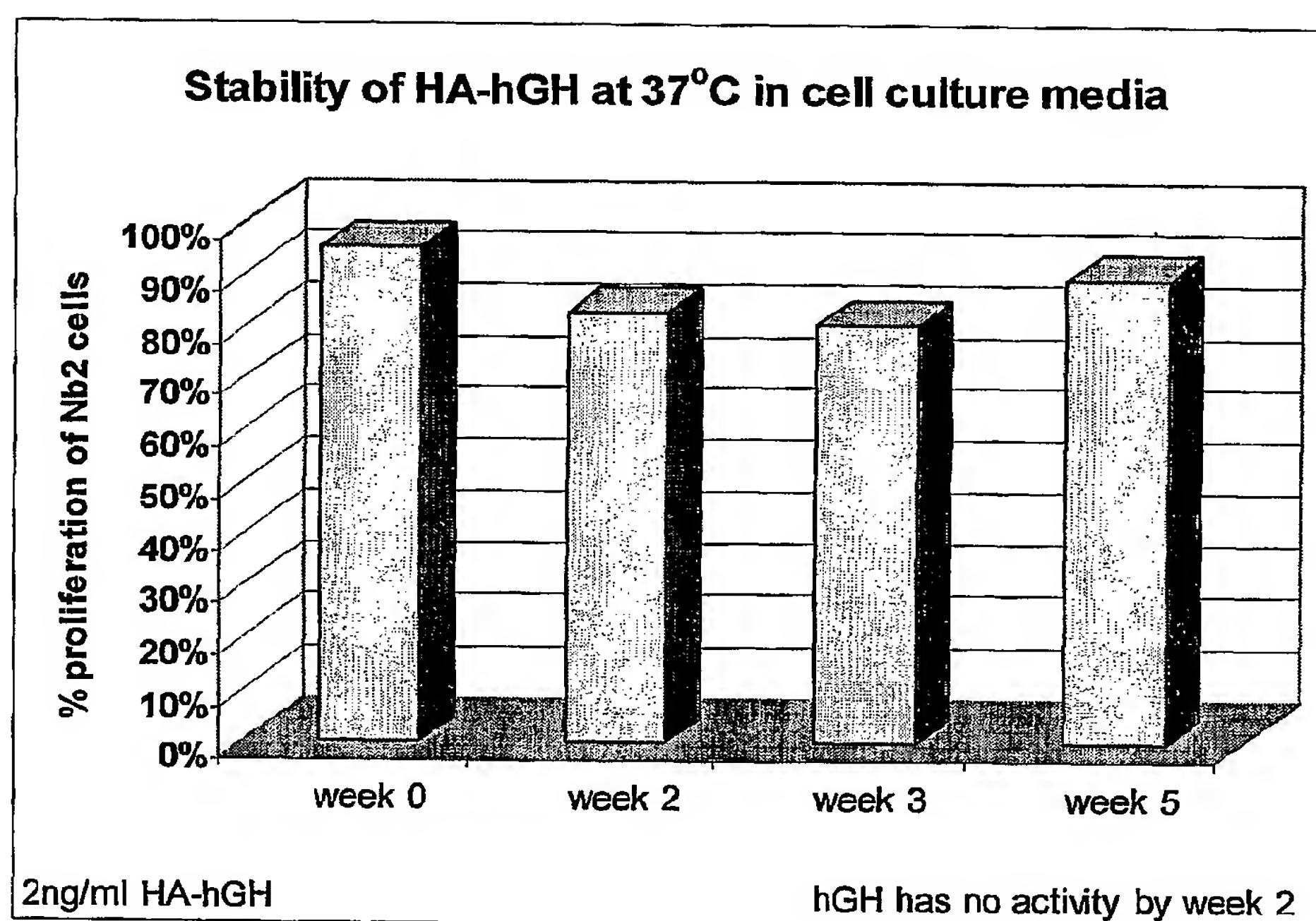
30. A composition comprising the albumin fusion protein of any one of claims 1-29 and a pharmaceutically acceptable carrier.

31. A kit comprising the composition of claim 30.
32. A method of treating a disease or disorder in a patient, comprising the step of administering the albumin fusion protein of any one of claims 1-29.
  - 5
33. The method of claim 32, wherein the disease or disorder comprises indication:Y.
- 10 34. The method of claim 33, wherein the Therapeutic protein:X, or fragment or variant thereof, comprises IL-2 and the disease or disorder is selected from the group consisting of: metastatic renal cell carcinoma; metastatic melanoma; malignant melanoma; renal cell carcinoma; HIV infection; inflammatory bowel disorder; Kaposi's sarcoma; leukaemia; multiple sclerosis; rheumatoid arthritis; transplant rejection; type 1 diabetes mellitus; lung cancer; acute myeloid leukaemia; hepatitis C; non-hodgkin's lymphoma; and ovarian cancer.
  - 15
35. A method of treating a patient with a disease or disorder that is modulated by Therapeutic protein:X, comprising the step of administering an effective amount of the albumin fusion protein of any one of claims 1-29.
  - 20
36. The method of claim 35, wherein the disease or disorder is indication:Y.
37. The method of claim 36, wherein the Therapeutic protein:X, or fragment or variant thereof, is IL-2 and the disease or disorder is selected from the group consisting of: metastatic renal cell carcinoma; metastatic melanoma; malignant melanoma; renal cell carcinoma; HIV infection; inflammatory bowel disorder; Kaposi's sarcoma; leukaemia; multiple sclerosis; rheumatoid arthritis; transplant rejection; type 1 diabetes mellitus; lung
  - 25

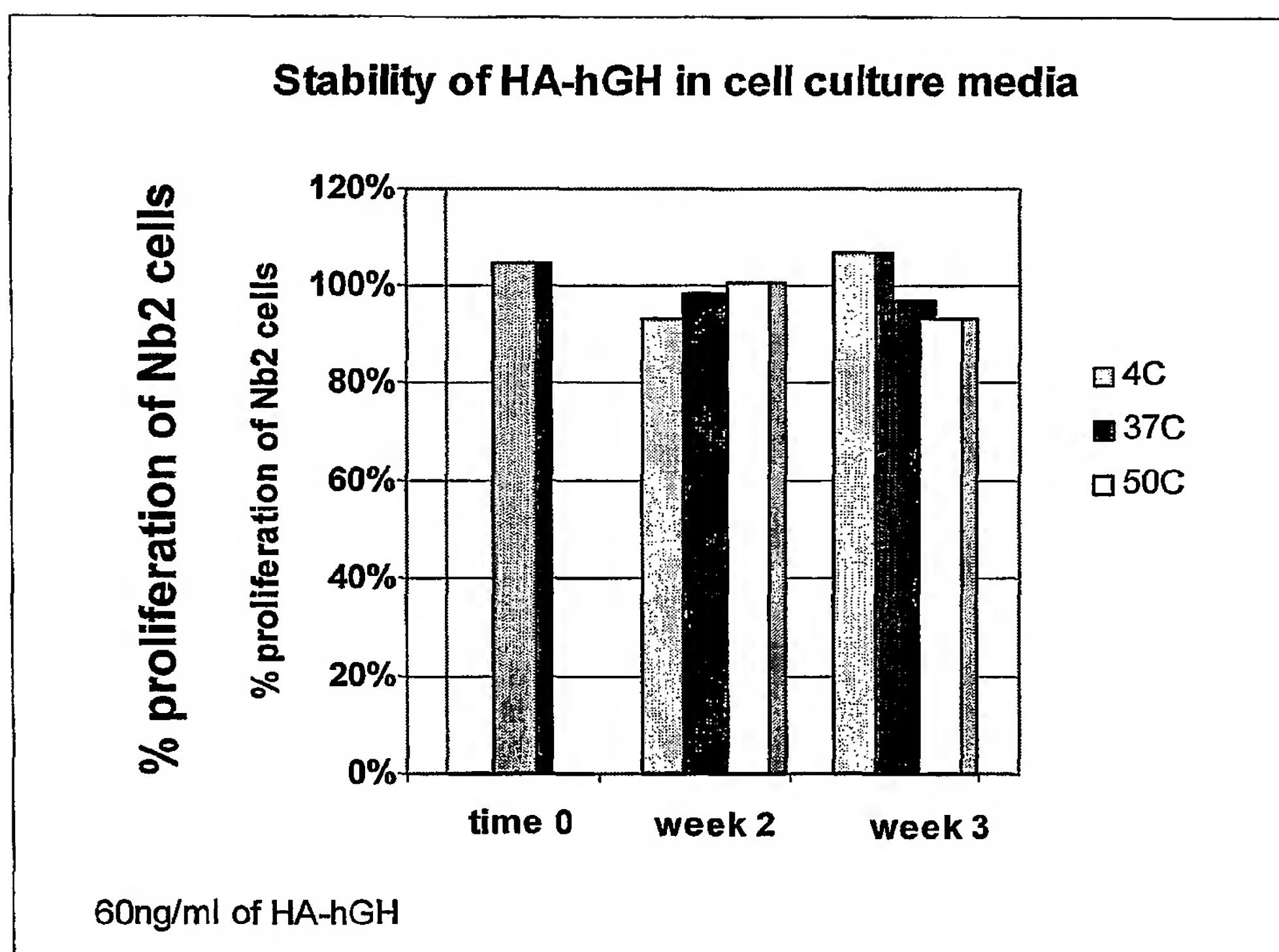
cancer; acute myeloid leukaemia; hepatitis C; non-hodgkin's lymphoma; and ovarian cancer.

38. A method of extending the shelf life of Therapeutic protein:X comprising the step of fusing the Therapeutic protein:X, or fragment or variant thereof, to albumin or a fragment or variant thereof of albumin sufficient to extend the shelf-life of the Therapeutic protein:X, or fragment or variant thereof, compared to the shelf-life of the Therapeutic protein:X, or fragment or variant thereof, in an unfused state.  
5
39. A nucleic acid molecule comprising a polynucleotide sequence encoding the albumin fusion protein of any one of claims 1-29.  
10
40. A vector comprising the nucleic acid molecule of claim 39.
41. A host cell comprising the nucleic acid molecule of claim 39.

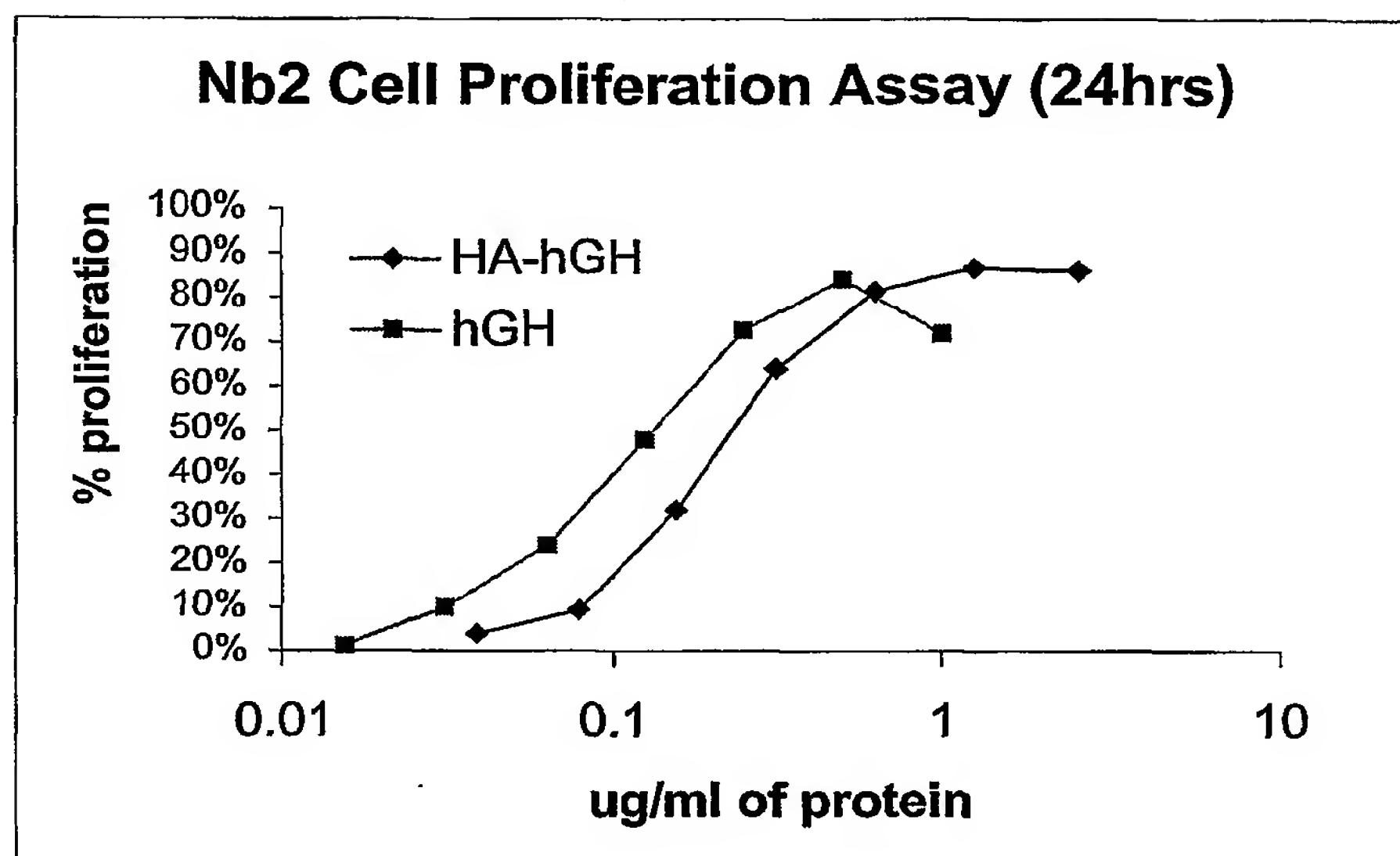
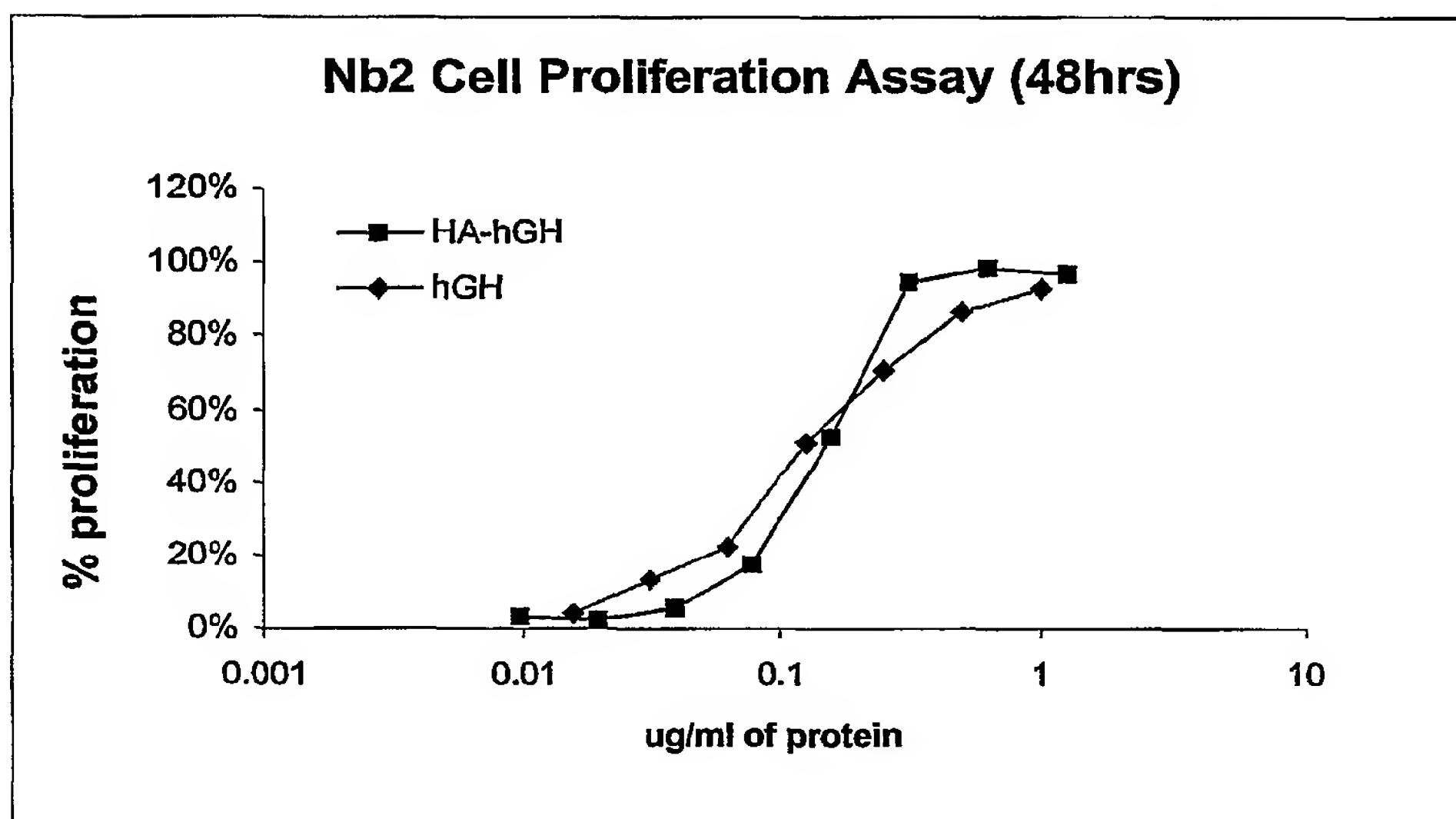
1/20

**Figure 1**

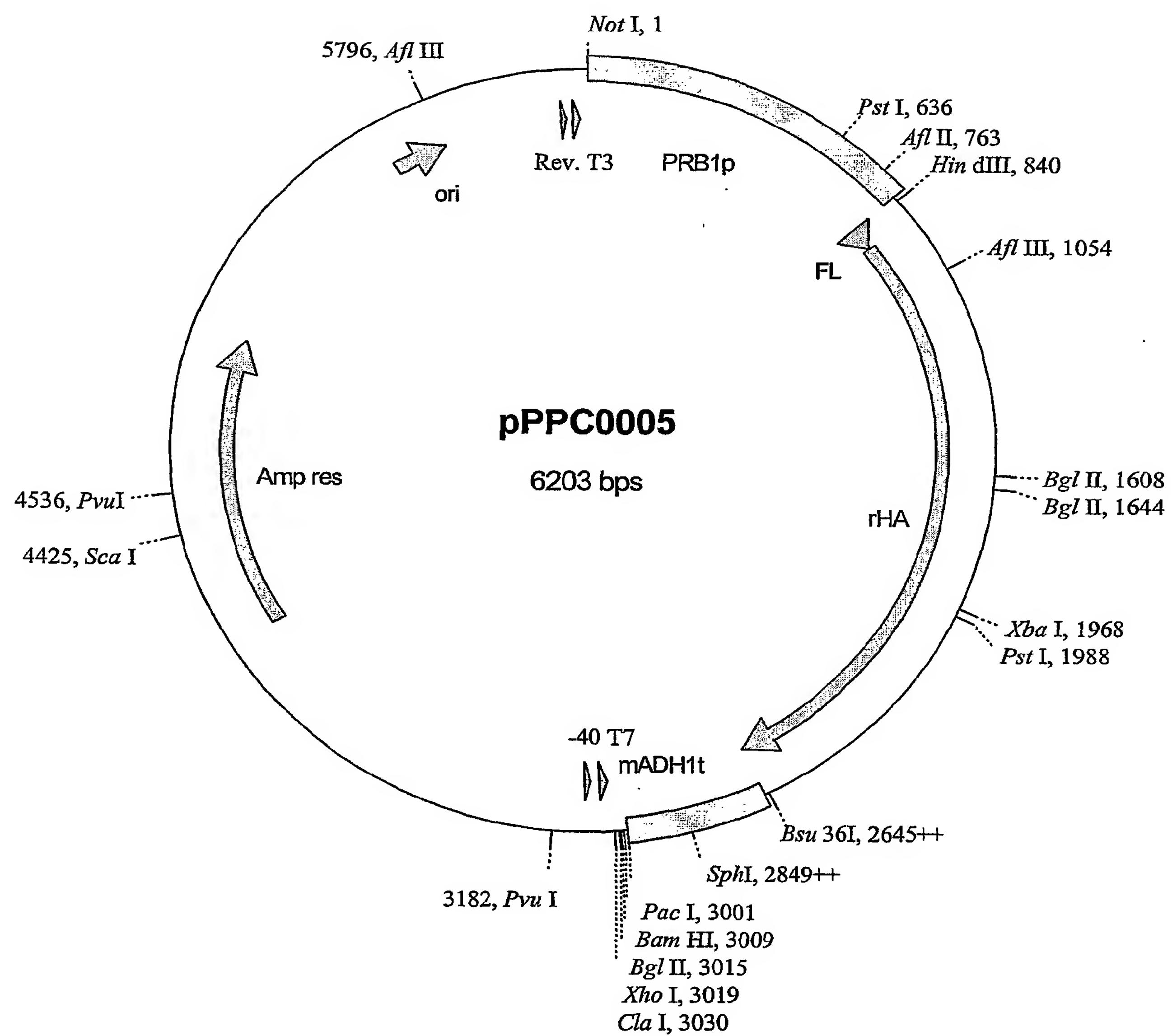
2/20

**Figure 2**

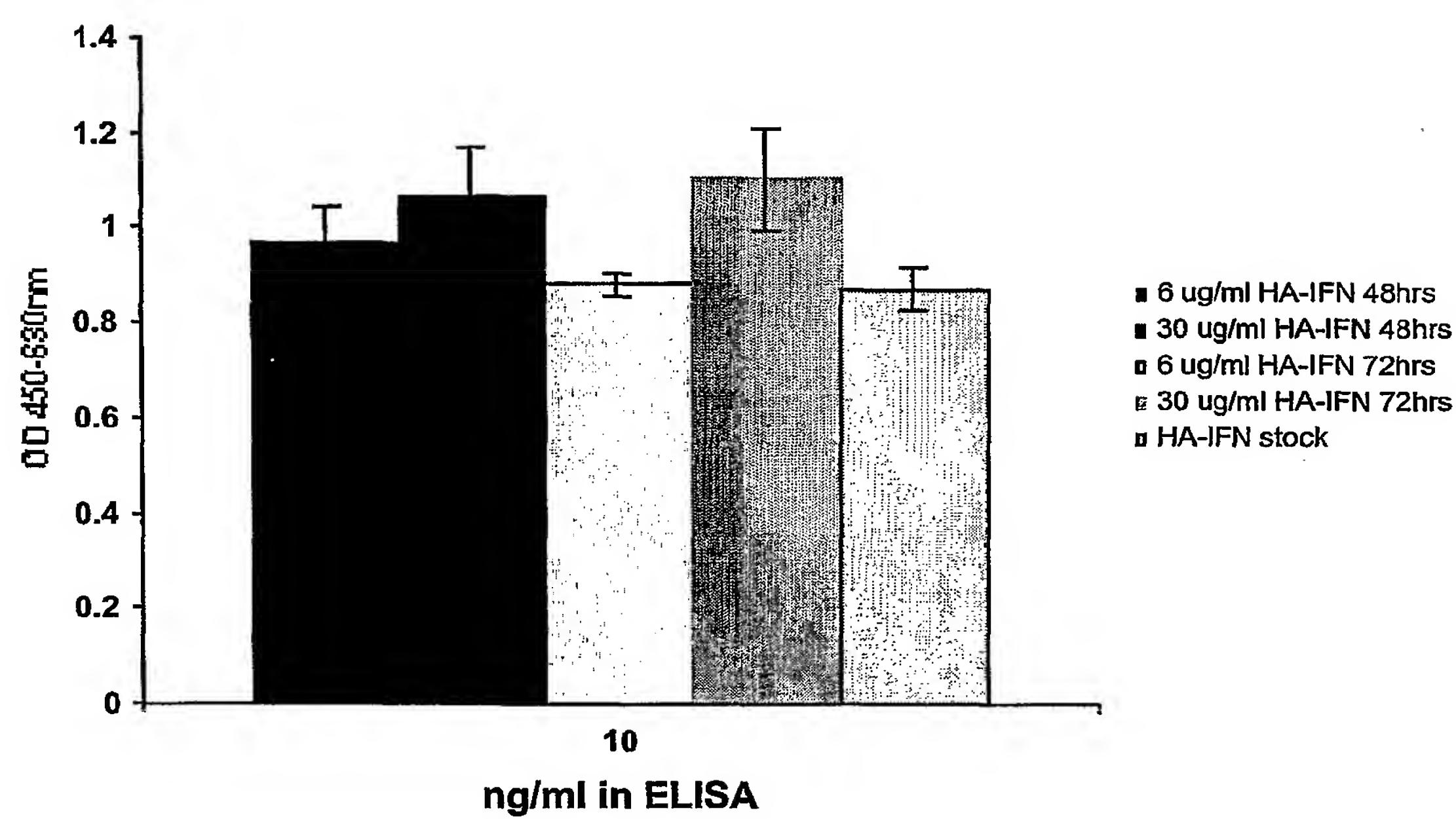
3/20

**Figure 3A****Figure 3B**

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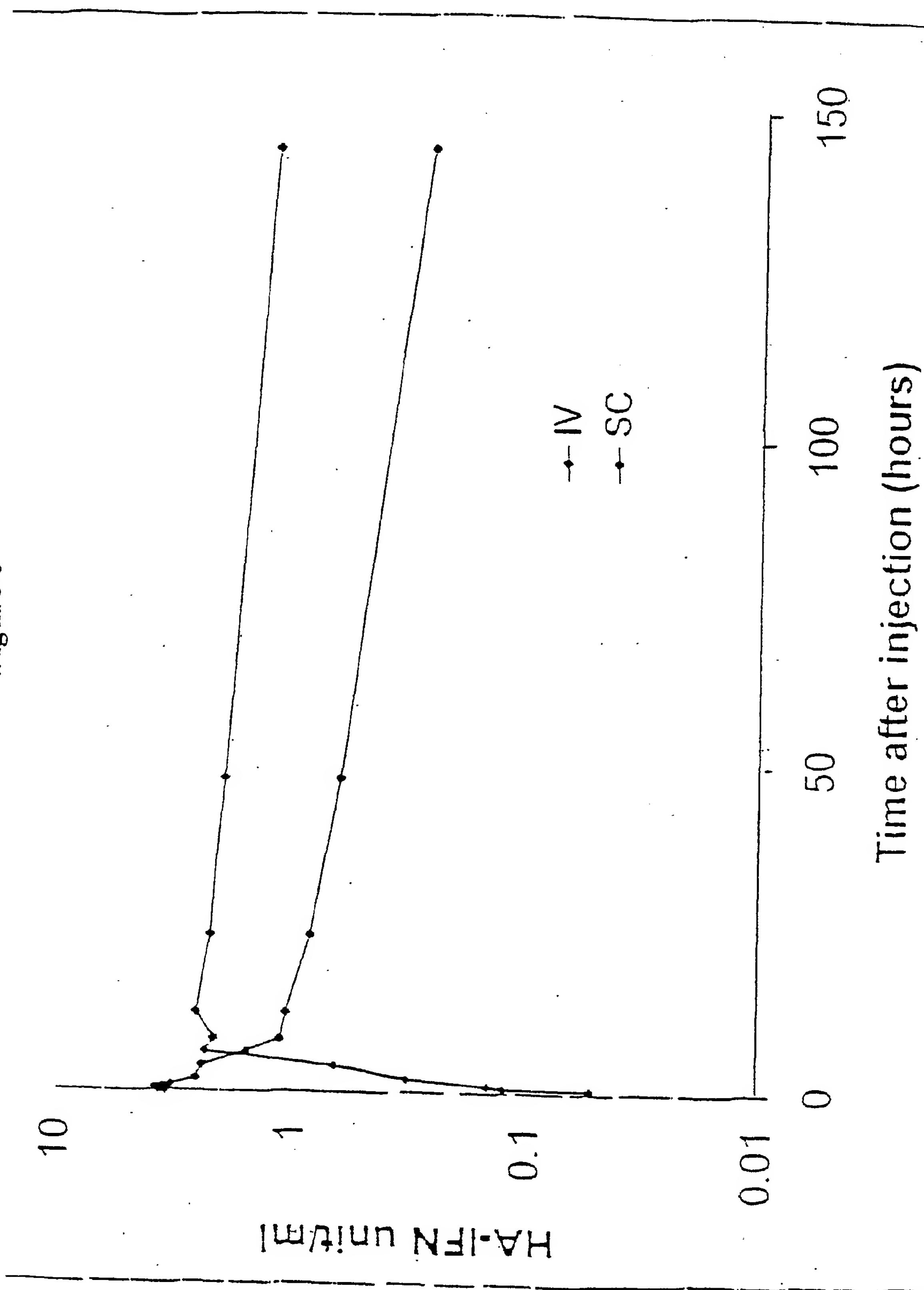
**Figure 4**

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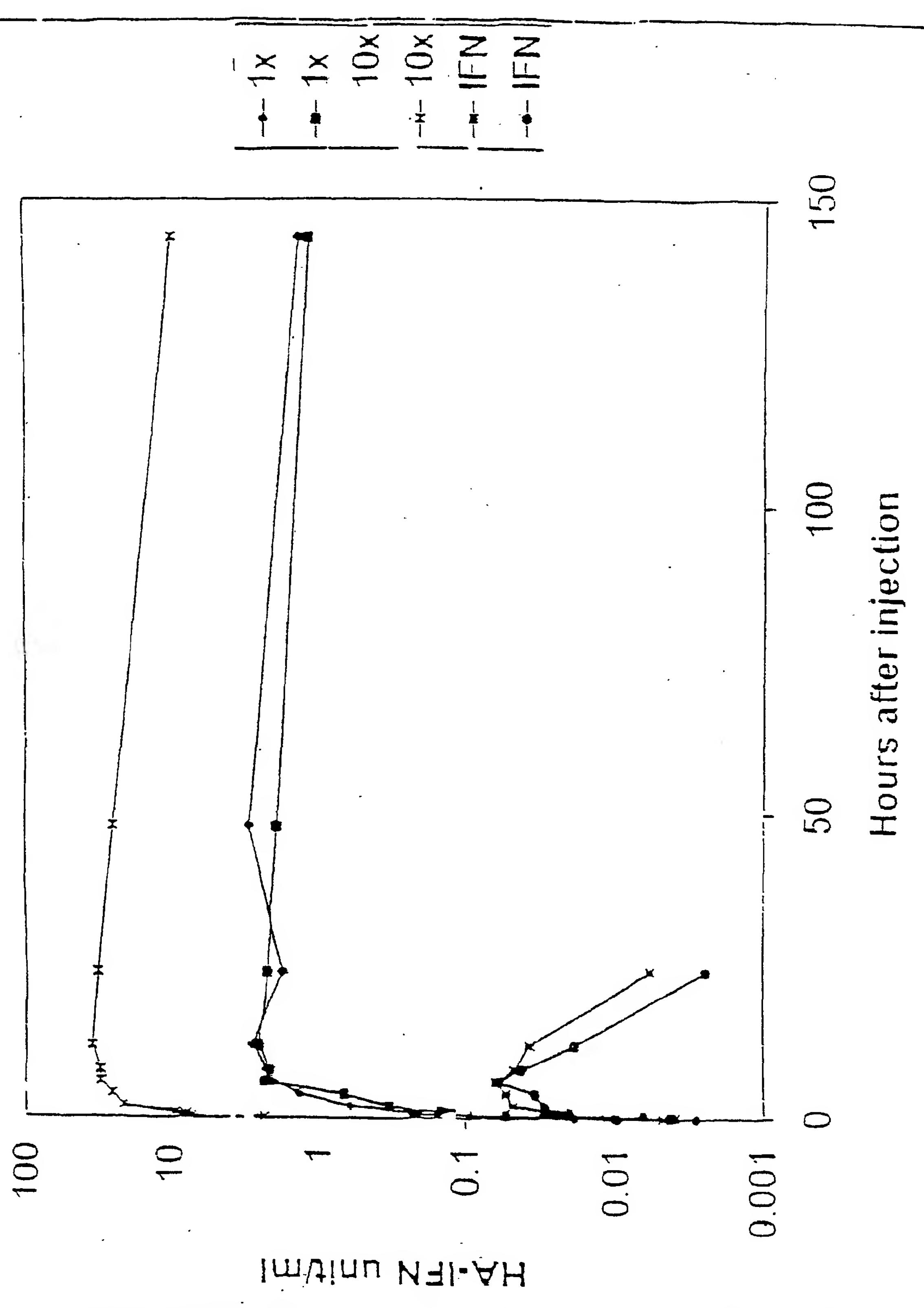
**Figure 5**

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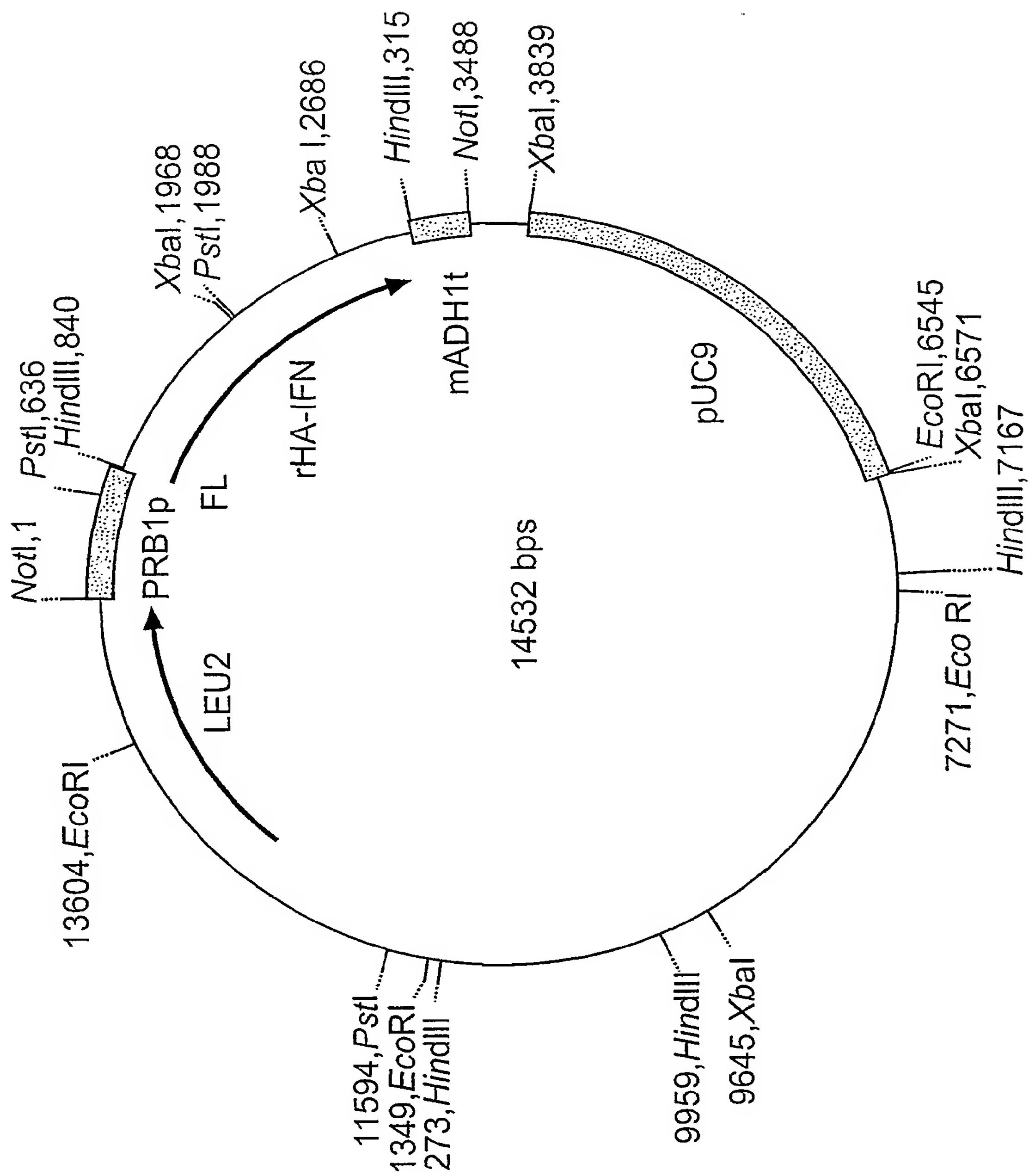
Figure 6



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**FIG. 8**

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## Localisation of ‘Loops’ based on the HA Crystal Structure which could be used for Mutation/Insertion

<b>Loop</b>		<b>Loop</b>	
I	Val154-Asn61	VII	Glu280-His288
II	Thr76-Asp89	VIII	Ala362-Glu368
III	Ala92-Glu100	IX	Lys439-Pro447
IV	Gln170-Ala176	X	Val462-Lys475
V	His247-Glu252	XI	Thr478-Pro486
VI	Glu266-Glu277	XII	Lys560-Thr566

**Figure 9**

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**Examples of Modifications to Loop IV****a. Randomisation of Loop IV.**

IV

151 APELLFFAKR YKAAFTECCQ AADKAACLLP KLDELRDEGK ASSAKQRLKC  
 HHHHHHHHHHHH HHHHHHHHHHHH HHHHHH HHHHHHHHHHHH HHHHHHHHHHHH

IV

151 APELLFFAKR YKAAFTECCX XXXXXXCLLP KLDELRDEGK ASSAKQRLKC  
 HHHHHHHHHHHH HHHHHHHHHHHH HHHHHH HHHHHHHHHHHH HHHHHHHHHHHH

**X** represents the mutation of the natural amino acid to any other amino acid. One, more or all of the amino acids can be changed in this manner. This figure indicates all the residues have been changed.

**b. Insertion (or replacement) of Randomised sequence into Loop IV.**

$(X)_n$

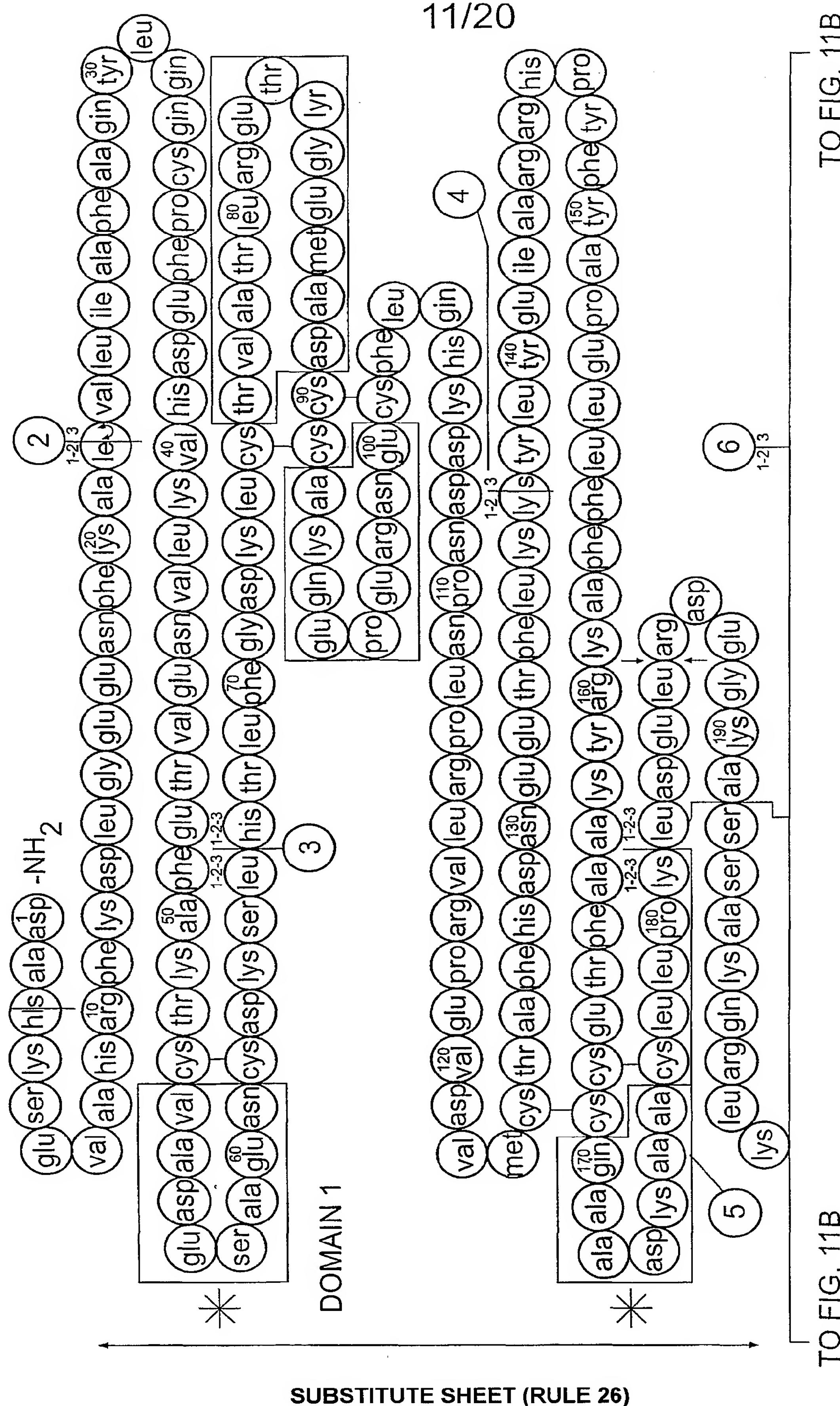
↓

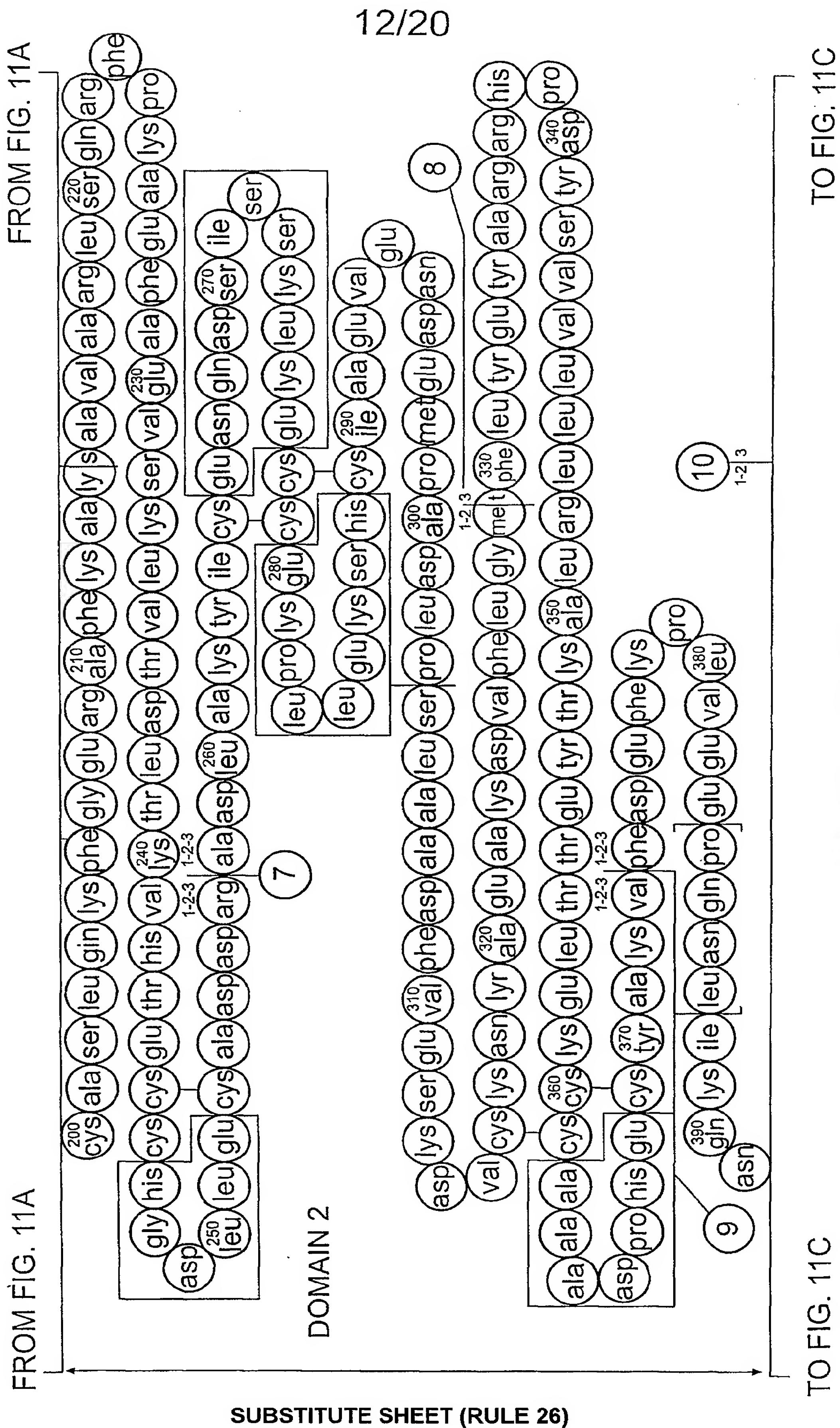
IV

151 APELLFFAKR YKAAFTECCQ AADKAACLLP KLDELRDEGK ASSAKQRLKC  
 HHHHHHHHHHHH HHHHHHHHHHHH HHHHHH HHHHHHHHHHHH HHHHHHHHHHHH

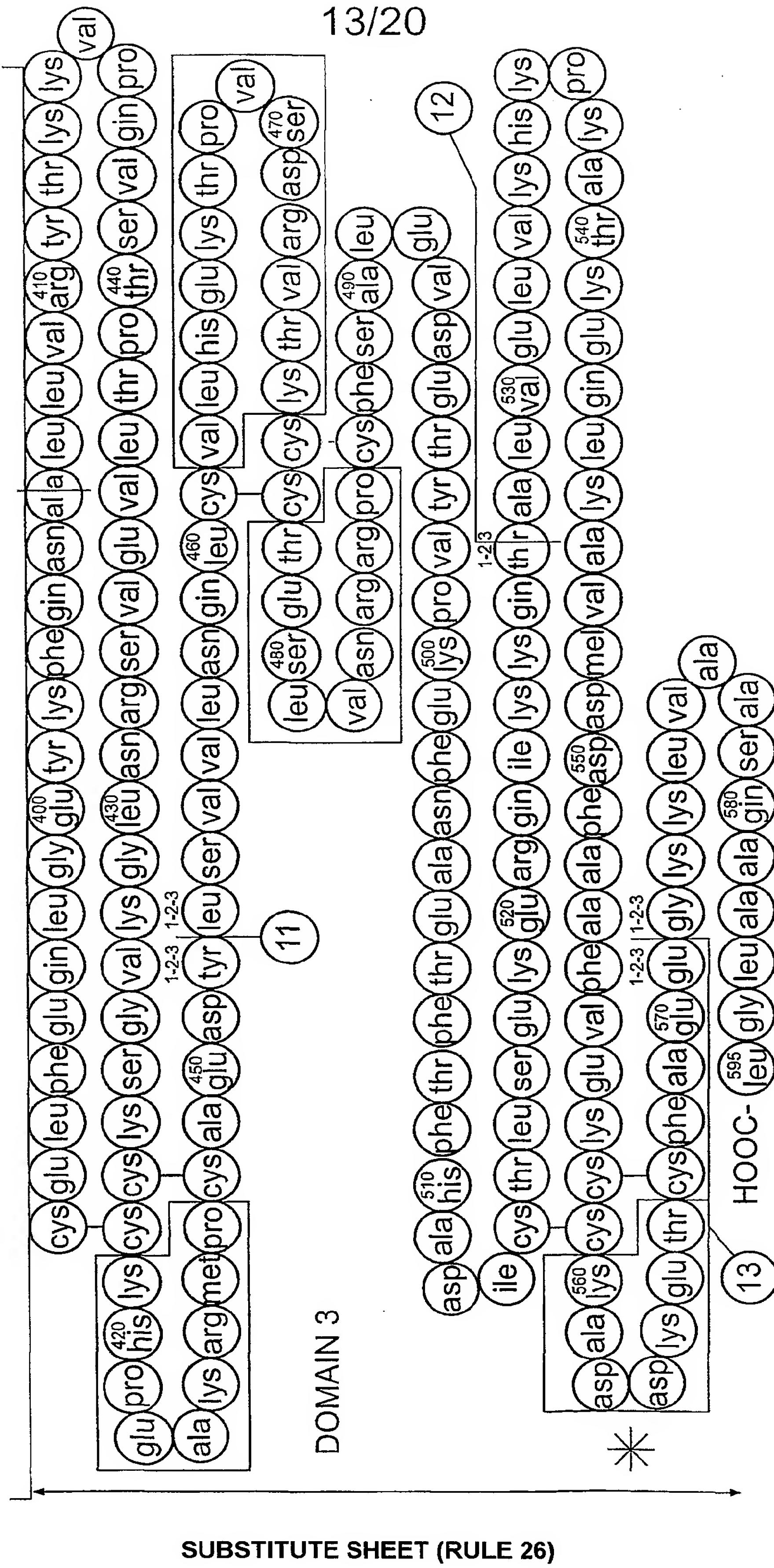
The insertion can be at any point on the loop and the length a length where n would typically be 6, 8, 12, 20 or 25.

**Figure 10**

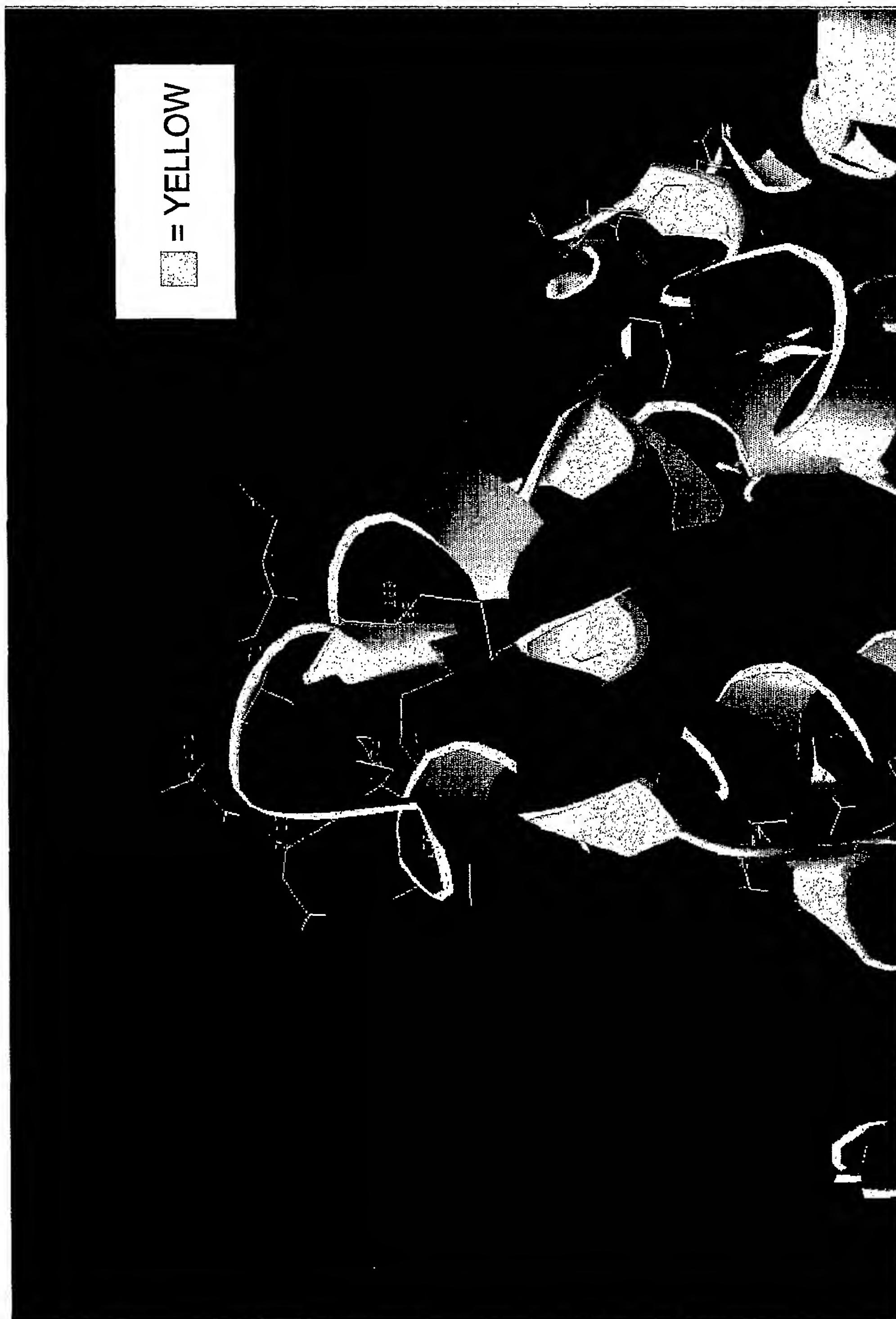
**FIG. 11A**



FROM FIG. 11B

**FIG. 11C**

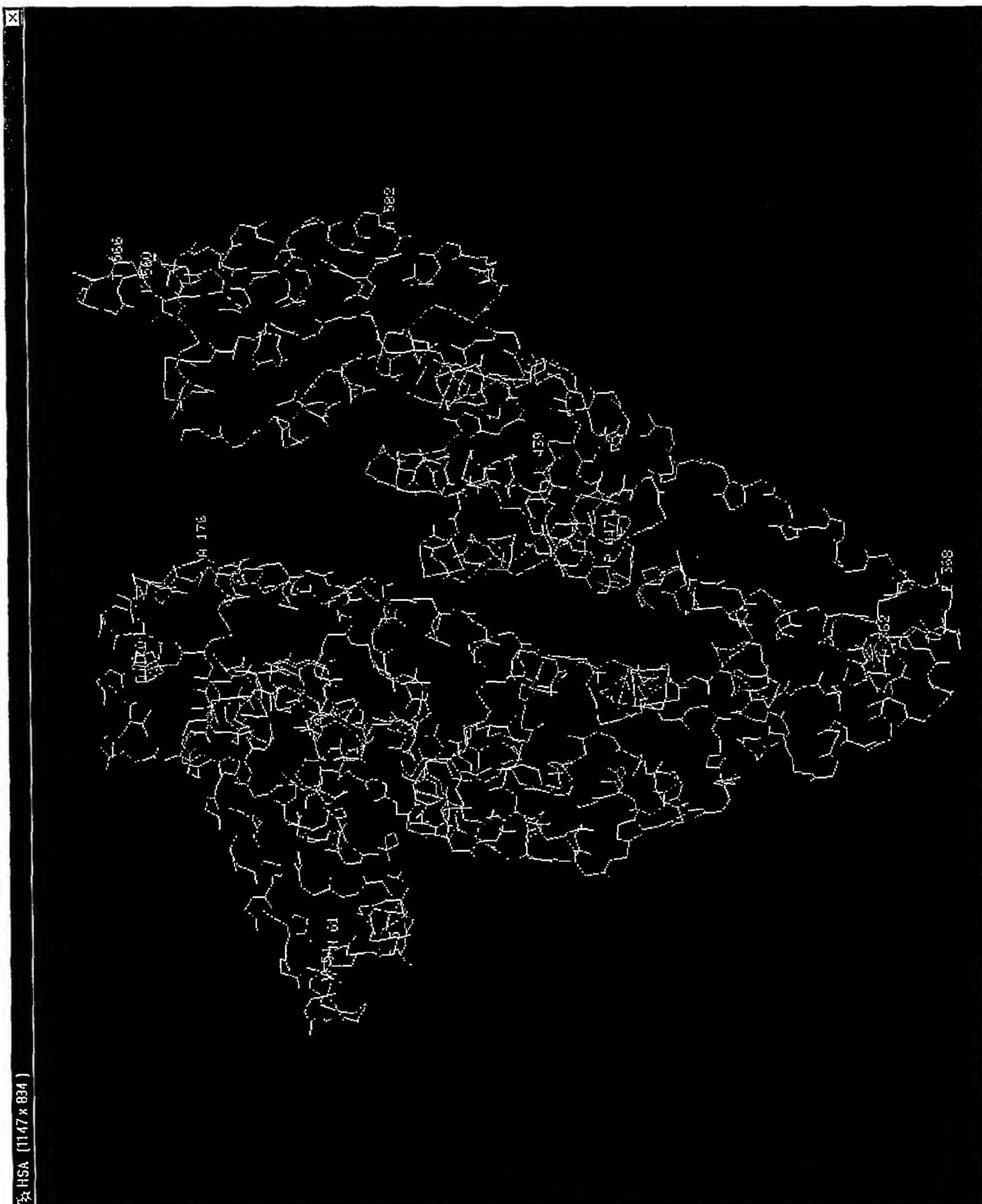
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DISULFIDE BONDS SHOWN IN YELLOW

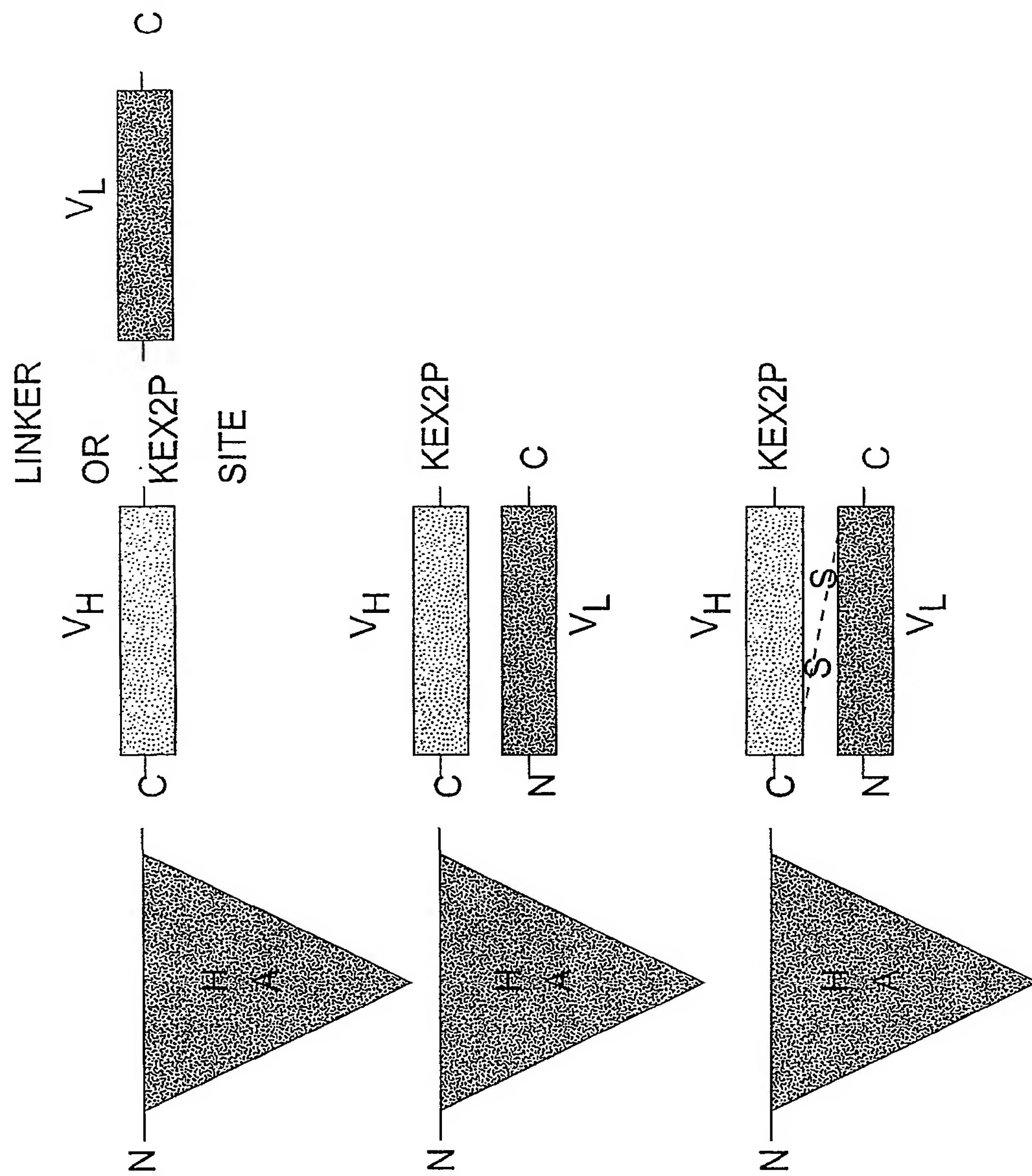
**FIG. 12:**  
*LOOP IV GLUT 170-A176*

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# **FIG. 13 TERTIARY STRUCTURE OF HA**

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**FIG. 14**

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1	GAT	GCA	CAC	AAG	AGT	GAG	GTT	GCT	CAT	CGG	TTT	AAA	GAT	TTC	GGA	GAA	GAA	AAT	TTC	AAA	60	
1	D	A	H	K	S	E	V	A	H	R	F	K	D	L	G	E	E	N	F	K	20	
61	GCC	TRG	GTG	TTG	ATT	GCC	TTT	GCT	CAG	TAT	CTT	CAG	CAG	TGT	CCA	TTT	GAA	GAT	CAT	GTA	120	
21	A	L	V	L	I	A	F	A	Q	Y	L	Q	Q	C	P	F	E	D	H	V	40	
121	AAA	TTA	TRG	AAT	GAA	GTA	ACT	GAA	TTT	GCA	AAA	ACA	TGT	GTT	GCT	GAT	GAG	TCA	GCT	GAA	180	
41	K.	L	V	N	E	V	T	E	F	A	K	T	C	V	A	D	E	S	A	E	60	
181	AAT	TGT	GAC	AAA	TCA	CTT	CAT	ACC	CTT	TTT	GGG	GAC	AAA	TTA	TGC	ACA	GTT	GCA	ACT	CTT	240	
61	N	C	D	K	S	L	H	T	L	F	G	D	K	L	C	T	V	A	T	L	80	
241	CGT	GAA	ACC	TAT	GGT	GAA	ATG	GCT	GAC	TGC	TGT	GCA	AAA	CAA	GAA	CCT	GAG	AGA	AAT	GAA	300	
81	R	E	T	Y	G	E	M	A	D	C	C	A	K	Q	E	P	E	R	N	E	100	
301	TGC	TTC	TRG	CAA	CAC	AAA	GAT	GAC	AAC	CCA	AAC	CTC	CCC	CGA	TTG	GTC	AGA	CCA	GAG	GTT	360	
101	C	F	L	Q	H	K	D	D	N	P	N	L	P	R	L	V	R	P	E	V	120	
361	GAT	GTG	ATG	TGC	ACT	GCT	TTT	CAT	GAC	AAT	GAA	GAG	ACA	TTC	TTG	AAA	AAA	TAC	TTA	TAT	420	
121	D	V	M	C	T	A	F	H	D	N	E	E	T	F	L	K	K	Y	L	Y	140	
421	GAA	ATT	GCC	AGA	AGA	CAT	CCT	TAC	TTT	TAT	GCC	CCG	GAA	CTC	CTT	TTT	GCT	TTT	GCT	AAA	AGG	480
141	E	I	A	R	R	H	P	Y	F	Y	A	P	E	L	L	F	F	A	K	R	160	

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481	TAT	AAA	GCT	TTT	ACA	GAA	TGT	TGC	CAA	GCT	GCT	GAT	AAA	GCT	GCC	TGC	CTG	TTG	CCA	540	
161	Y	K	A	A	F	T	E	C	C	Q	A	D	K	A	A	C	L	L	P	180	
541	AAG	CTC	GAT	GAA	CTT	CGG	GAT	GAA	GGG	AAG	GCT	TCG	TCT	GCC	AAA	CAG	AGA	CTC	AAA	TGT	600
181	K	L	D	E	L	R	D	E	G	K	A	S	S	A	K	Q	R	L	K	C	200
601	GCC	AGT	CTC	CAA	AAA	TTT	GGA	GAA	AGA	GCT	TTC	AAA	GCA	TGG	GCA	GTC	GCT	CGC	CTG	AGC	660
201	A	S	L	Q	K	F	G	E	R	A	F	K	A	W	A	V	A	R	L	S	220
661	CAG	AGA	TTT	CCC	AAA	GCT	GAG	TTT	GCA	GAA	GTT	TCC	AAG	TTA	GTG	ACA	GAT	CTT	ACC	AAA	720
221	Q	R	F	P	K	A	E	F	A	E	V	S	K	L	V	T	D	L	T	K	240
721	GTC	CAC	ACG	GAA	TGC	TGC	CAT	GGA	GAT	CTG	CTT	GAA	TGT	GCT	GAT	GAC	AGG	GCG	GAC	CTT	780
241	V	H	T	E	C	C	H	G	D	L	L	E	C	A	D	D	R	A	D	L	260
781	GCC	AAG	TAT	ATC	TGT	GAA	AAT	CAG	GAT	TCG	ATC	TCC	AGT	AAA	CTG	AAG	GAA	TGC	TGT	GAA	840
261	A	K	Y	I	C	E	N	Q	D	S	I	S	S	K	L	K	E	C	C	E	280
841	AAA	CCT	CTG	TTG	GAA	AAA	TCC	CAC	TGC	ATT	GCC	GAA	GTA	GAT	GAG	ATG	CCT	GCT	900		
281	K	P	L	L	E	K	S	H	C	I	A	E	V	E	N	D	E	M	P	A	300
901	GAC	TTG	CCT	TCA	TTA	GCT	GCT	GAT	TTT	GTG	GAA	AGT	AAG	GAT	GTT	TGC	AAA	AAC	TAT	GCT	960
301	D	L	P	S	L	A	A	D	F	V	E	S	K	D	V	C	K	N	Y	A	320

Figure 15B

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961 GAG GCA AAG GAT GTC TTC CTG GGC ATG TTT TTG TAT GAA TAT GCA AGA AGG CAT CCT GAT 1020  
 321 E A K D V F L G M F L Y E Y A R R H P D 340

1021 TAC TCT GTC GTG CTG CTG AGA CTT GCC AAG ACA TAT GAA ACC ACT CTA GAG AAG TGC 1080  
 341 Y S V V L L R L A K T Y E T T L E K C 360

1081 TGT GCC GCT GCA GAT CCT CAT GAA TGC TAT GCC AAA GTG TTC GAT GAA TTT AAA CCT CTT 1140  
 361 C A A D P H E C Y A K V F D E F K P L 380

1141 GTC GAA GAG CCT CAG AAT TTA ATC AAA CAA AAC TGT GAG CTT TTT GAG CAG CTT GGA GAG 1200  
 381 V E E P Q N L I K Q N C E L F E Q L G E 400

1201 TAC AAA TTC CAG AAT GCG CTA TTA GTT CGT TAC ACC AAG AAA GTA CCC CAA GTG TCA ACT 1260  
 401 Y K F Q N A L V R Y T K K V P Q V S T 420

1261 CCA ACT CTT GTA GAG GTC TCA AGA AAC CTA GGA AAA GTG GGC AGC AAA TGT TGT AAA CAT 1320  
 421 P T L V E V S R N L G K V G S K C C K H 440

1321 CCT GAA GCA AAA AGA ATG CCC TGT GCA GAA GAC TAT CTA TCC GTG GTC AAC CAG TTA 1380  
 441 P E A K R M P C A E D Y L S V V L N Q L 460

1381 TGT GTG TTG CAT GAG AAA ACG CCA GTC AGT GAC AGA GTC ACA AAA TGC TGC ACA GAG TCC 1440  
 461 C V L H E K T P V S D R V T K C C T E S 480

Figure 15C

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1441	TTG	GTG	AAC	AGG	CGA	CCA	TGC	TTT	TCA	GCT	CTG	GAA	GAT	GAA	ACA	TAC	GTT	CCC	AAA	1500	
481	I	V	N	R	R	P	C	F	S	A	L	E	V	D	E	T	Y	V	P	K	500
1501	GAG	TTT	AAT	GCT	GAA	ACA	TTC	ACC	TTC	CAT	GCA	GAT	ATA	TGC	ACA	CTT	TCT	GAG	AAG	GAG	1560
501	E	F	N	A	E	T	F	T	F	H	A	D	T	C	T	L	S	E	K	E	520
1561	AGA	CAA	ATC	AAG	AAA	CAA	ACT	GCA	CTT	GTT	GAG	CTT	GTC	AAA	CAC	AAG	CCC	AAG	GCA	ACA	1620
521	R	Q	I	K	K	Q	T	A	L	V	E	L	V	K	H	P	K	A	T	540	
1621	AAA	GAG	CAA	CTG	AAA	GCT	GTT	ATG	GAT	TTC	GCA	GCT	TTT	GTA	GAG	AAG	TGC	TGC	AAG	1680	
541	K	E	Q	L	K	A	V	M	D	D	F	A	A	F	V	E	K	C	C	K	560
1681	GCT	GAC	GAT	AAG	GAG	ACC	TGC	TTT	GCC	GAG	GAG	GGT	AAA	AAA	CTT	GTT	GCT	GCA	AGT	CAA	1740
561	A	D	D	K	E	T	C	F	A	E	E	G	K	K	L	V	A	A	S	Q	580
1741	GCT	GCC	TTA	GGC	TTA	TAA	CAT	CTA	CAT	TIA	AAA	GCA	TCT	CAG	1782						
581	A	A	L	G	L	*														585	

Figure 15D

## SEQUENCE LISTING

<110> Human Genome Science, Inc.  
Principia Pharmaceutical Corporation

<120> Albumin Fusion Proteins

<130> PF543PCT

<140> Unassigned  
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<150> 60/229,358  
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<150> 60/256,931  
<151> 2000-12-21

<150> 60/199,384  
<151> 2000-04-25

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Ile Ser Ala Asp Ala His Lys Ser  
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31

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ac 62

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1 5 10 15

gaa aat ttc aaa gcc ttg gtg ttg att gcc ttt gct cag tat ctt cag 96  
Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln  
20 25 30

cag tgt cca ttt gaa gat cat gta aaa tta gtg aat gaa gta act gaa 144  
Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu  
35 40 45

ttt gca aaa aca tgt gtt gct gat gag tca gct gaa aat tgt gac aaa 192  
Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys  
50 55 60

tca ctt cat acc ctt ttt gga gac aaa tta tgc aca gtt gca act ctt 240  
Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu  
65 70 75 80

cgt gaa acc tat ggt gaa atg gct gac tgc tgt gca aaa caa gaa cct 288  
Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro  
85 90 95

gag aga aat gaa tgc ttc ttg caa cac aaa gat gac aac cca aac ctc 336  
Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu  
100 105 110

ccc cga ttg gtg aga cca gag gtt gat gtg atg tgc act gct ttt cat 384

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His			
115	120	125	
gac aat gaa gag aca ttt ttg aaa aaa tac tta tat gaa att gcc aga			432
Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg			
130	135	140	
aga cat cct tac ttt tat gcc ccg gaa ctc ctt ttc ttt gct aaa agg			480
Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg			
145	150	155	160
tat aaa gct gct ttt aca gaa tgt tgc caa gct gct gat aaa gct gcc			528
Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala			
165	170	175	
tgc ctg ttg cca aag ctc gat gaa ctt cg gat gaa ggg aag gct tcg			576
Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser			
180	185	190	
tct gcc aaa cag aga ctc aaa tgt gcc agt ctc caa aaa ttt gga gaa			624
Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu			
195	200	205	
aga gct ttc aaa gca tgg gca gtg gct cgc ctg agc cag aga ttt ccc			672
Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro			
210	215	220	
aaa gct gag ttt gca gaa gtt tcc aag tta gtg aca gat ctt acc aaa			720
Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys			
225	230	235	240
gtc cac acg gaa tgc tgc cat gga gat ctg ctt gaa tgt gct gat gac			768
Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp			
245	250	255	
agg gcg gac ctt gcc aag tat atc tgt gaa aat cag gat tcg atc tcc			816
Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser			
260	265	270	
agt aaa ctg aag gaa tgc tgt gaa aaa cct ctg ttg gaa aaa tcc cac			864
Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His			
275	280	285	
tgc att gcc gaa gtg gaa aat gat gag atg cct gct gac ttg cct tca			912
Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser			
290	295	300	
tta gct gct gat ttt gtt gaa agt aag gat gtt tgc aaa aac tat gct			960
Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala			
305	310	315	320
gag gca aag gat gtc ttc ctg ggc atg ttt ttg tat gaa tat gca aga			1008
Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg			
325	330	335	
agg cat cct gat tac tct gtc gtg ctg ctg aga ctt gcc aag aca			1056
Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr			
340	345	350	
tat gaa acc act cta gag aag tgc tgt gcc gct gca gat cct cat gaa			1104

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu			
355	360	365	
tgc tat gcc aaa gtg ttc gat gaa ttt aaa cct ctt gtg gaa gag cct			1152
Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro			
370	375	380	
cag aat tta atc aaa caa aac tgt gag ctt ttt gag cag ctt gga gag			1200
Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu			
385	390	395	400
tac aaa ttc cag aat gcg cta tta gtt cgt tac acc aag aaa gta ccc			1248
Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro			
405	410	415	
caa gtg tca act cca act ctt gta gag gtc tca aga aac cta gga aaa			1296
Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys			
420	425	430	
gtg ggc agc aaa tgt tgt aaa cat cct gaa gca aaa aga atg ccc tgt			1344
Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys			
435	440	445	
gca gaa gac tat cta tcc gtg gtc ctg aac cag tta tgt gtg ttg cat			1392
Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His			
450	455	460	
gag aaa acg cca gta agt gac aga gtc aca aaa tgc tgc aca gag tcc			1440
Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser			
465	470	475	480
ttg gtg aac agg cga cca tgc ttt tca gct ctg gaa gtc gat gaa aca			1488
Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr			
485	490	495	
tac gtt ccc aaa gag ttt aat gct gaa aca ttc acc ttc cat gca gat			1536
Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp			
500	505	510	
ata tgc aca ctt tct gag aag gag aga caa atc aag aaa caa act gca			1584
Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala			
515	520	525	
ctt gtt gag ctt gtg aaa cac aag ccc aag gca aca aaa gag caa ctg			1632
Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu			
530	535	540	
aaa gct gtt atg gat gat ttc gca gct ttt gta gag aag tgc tgc aag			1680
Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys			
545	550	555	560
gct gac gat aag gag acc tgc ttt gcc gag gag ggt aaa aaa ctt gtt			1728
Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val			
565	570	575	
gct gca agt caa gct gcc tta ggc tta taacatctac atttaaaagc atctcag			1782
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580	585		

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Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu  
35 40 45  
Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys  
50 55 60  
Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu  
65 70 75 80  
Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro  
85 90 95  
Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu  
100 105 110  
Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His  
115 120 125  
Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg  
130 135 140  
Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg  
145 150 155 160  
Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala  
165 170 175  
Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser  
180 185 190  
Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu  
195 200 205  
Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro  
210 215 220  
Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys  
225 230 235 240  
Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp  
245 250 255  
Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser  
260 265 270  
Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His  
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser  
 290 295 300  
 Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala  
 305 310 315 320  
 Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg  
 325 330 335  
 Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr  
 340 345 350  
 Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu  
 355 360 365  
 Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro  
 370 375 380  
 Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu  
 385 390 395 400  
 Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro  
 405 410 415  
 Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys  
 420 425 430  
 Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys  
 435 440 445  
 Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His  
 450 455 460  
 Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser  
 465 470 475 480  
 Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr  
 485 490 495  
 Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp  
 500 505 510  
 Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala  
 515 520 525  
 Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu  
 530 535 540  
 Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys  
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 580 585

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tacaaaactta agagtccaat tagc 24

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<400> 24  
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<210> 25  
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32

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of the Therapeutic Protein

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33

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**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

- A.** The indications made below relate to the deposited microorganism or other biological material referred to in the description on page 37, line 14.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet

Name of depositary institution: American Type Culture Collection

Address of depositary institution (*including postal code and country*)  
10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit:

11 April 2001

Accession Number

PTA-3276

**C. ADDITIONAL INDICATIONS** (*leave blank if not applicable*)

This information is continued on an additional sheet

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** (*if the indications are not for all designated States*)

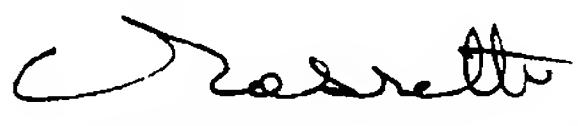
Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

**E. SEPARATE FURNISHING OF INDICATIONS** (*leave blank if not applicable*)

The indications listed below will be submitted to the International Bureau later (*specify the general nature of the indications e.g., "Accession Number of Deposit"*)

	For receiving Office use only			For International Bureau use only	
<input type="checkbox"/> This sheet was received with the international application	<input checked="" type="checkbox"/> This sheet was received by the International Bureau on 15 May 01				
Authorized officer	Authorized officer				

**ATCC Deposit No.: PTA-3276**

**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

**ATCC Deposit No.: PTA-3276**

**DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

**SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

**NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

- A.** The indications made below relate to the deposited microorganism or other biological material referred to in the description on page 37, line 14.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet

Name of depositary institution: American Type Culture Collection

Address of depositary institution (*including postal code and country*)  
10801 University Boulevard

Manassas, Virginia 20110-2209  
United States of America

Date of deposit

11 April 2001

Accession Number

PTA-3277

**C. ADDITIONAL INDICATIONS** (*leave blank if not applicable*)

This information is continued on an additional sheet

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** (*if the indications are not for all designated States*)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

**E. SEPARATE FURNISHING OF INDICATIONS** (*leave blank if not applicable*)

The indications listed below will be submitted to the International Bureau later (*specify the general nature of the indications e.g., "Accession Number of Deposit"*)

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Authorized officer		Authorized officer <i>Rosette</i>			

**ATCC Deposit No.: PTA-3277**

**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

**ATCC Deposit No.: PTA-3277**

**DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

**SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex 2 of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

**NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

- A.** The indications made below relate to the deposited microorganism or other biological material referred to in the description on page 37, line 14.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet

Name of depositary institution: American Type Culture Collection

Address of depositary institution (*including postal code and country*)

10801 University Boulevard  
Manassas, Virginia 20110-2209

United States of America

Date of deposit

11 April 2001

Accession Number

PTA-3278

**C. ADDITIONAL INDICATIONS** (*leave blank if not applicable*)

This information is continued on an additional sheet

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** (*if the indications are not for all designated States*)

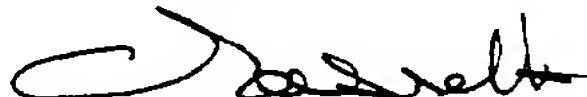
Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

**E. SEPARATE FURNISHING OF INDICATIONS** (*leave blank if not applicable*)

The indications listed below will be submitted to the International Bureau later (*specify the general nature of the indications e.g., "Accession Number of Deposit"*)

	For receiving Office use only			For International Bureau use only
<input type="checkbox"/> This sheet was received with the international application		<input checked="" type="checkbox"/> This sheet was received by the International Bureau on <u>15 May 01</u>		
Authorized officer		Authorized officer: 		

**ATCC Deposit No.: PTA-3278**

**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

**ATCC Deposit No.: PTA-3278**

**DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

**SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

**NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

**A.** The indications made below relate to the deposited microorganism or other biological material referred to in the description on page 37, line 14.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet

Name of depositary institution: American Type Culture Collection

Address of depositary institution (*including postal code and country*)  
10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit

11 April 2001

Accession Number

PTA-3279

**C. ADDITIONAL INDICATIONS** (*leave blank if not applicable*)

This information is continued on an additional sheet

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** (*If the indications are not for all designated States,* *Continued on additional sheets*)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

**E. SEPARATE FURNISHING OF INDICATIONS** (*leave blank if not applicable*)

The indications listed below will be submitted to the International Bureau later (*specify the general nature of the indications e.g., "Accession Number of Deposit"*)

	For receiving Office use only			For International Bureau use only
<input type="checkbox"/> This sheet was received with the international application		<input checked="" type="checkbox"/> This sheet was received by the International Bureau on: <i>15 May 01</i>		
Authorized officer		Authorized officer		

**ATCC Deposit No.: PTA-3279**

**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

**ATCC Deposit No.: PTA-3279**

**DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

**SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex 2 of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

**NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

## INTERNATIONAL SEARCH REPORT

International application No. PCT/US01/12008
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**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) : C07K 1/00; A01N 37/18  
US CL : 530/350; 514/2

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/350; 514/2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN: MEDLINE BIOSIS BIOTECHDS EMBASE CAPLUS  
WEST  
STIC COMMERCIAL DATABASE SEQUENCE SEARCH

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93/15199 A1 (RHONE-POULENC RORER S.A.) 05 August 1993, see abstract; Fig. 1, page ,3 lines 5 and 6, page 4, lines 25-31, and enclosed sequence alingment.	1-4, 6, 8, 18, 20-22, 38
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Y		5, 7, 19
X	WO 93/15211 A1 (RHONE-POULENC RORER S.A.) 05 August 1993, see abstract, Fig. 1, and enclosed sequence alignment.	1-4, 6, 8, 18, 20-22, 38
--		-----
Y		5,7,19
Y	WO 96/18412 A1 (BETH ISRAEL HOSPITAL ASSOCIATION) 20 June 1996, See abstract, page 8, lines 15-24, and 31-35; and page 9, lines 21 and 22.	1-8, 18-22, 38

Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principles or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means		
"P" document published prior to the international filing date but later than the priority date claimed		

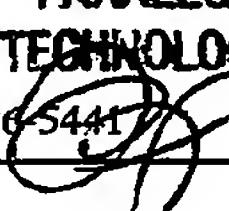
Date of the actual completion of the international search

09 JULY 2001

Date of mailing of the international search report

02 AUG 2001

Name and mailing address of the ISA/US  
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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/12008

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	YEH et al. Design of yeast-secreted albumin derivatives for human therapy. Proc. Nat. Acad. Sci. USA. March 1992. Vol. 69, pages 1904-1908, see entire document, especially abstract, page 1905, column 1, lines 14-17 and Fig. 1, panel A, and page 1096, column 1, lines 13-15 of first full paragraph.	1-4, 6, 8, 18, 20-22, 38
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Y	Database MEDLINE, Accession No. 1999248670, LEE et al. Preparation and characterization of polyethylene-glycol-modified salmon calcitonins. Pharm. Dev. Tech. May 1999. Vol. 4, No. 2, pages 269-275, abstract only.	5, 7, 18-22
Y	Database MEDLINE, Accession No. 97290787, TAKAHASHI et al. Production of bioactive salmon calcitonin from the nonendocrine cell lines COS-7 and CHO. Peptides (1997). Vol. 18, no. 3, pages 439-444, abstract only.	1-8, 18-22, 38

**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/US01/12008

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3.  Claims Nos.: 9-17, 23-37, 39-41 because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-8, 18-22, 38

**Remark on Protest**  

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**

International application No. PCT/US01/12008
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**BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING**  
This ISA found multiple inventions as follows:

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be searched, the appropriate additional search fees must be paid. The species are as follows:

calcitonin, growth hormone releasing factor, IL-2, IL-2 fusion protein, IGF-1, interferon beta, and parathyroid hormone.

The claims are deemed to correspond to the species listed above in the following manner:

Claims 1-6, 8, 18-22, and 38 are generic to all species. Claim 7 is generic to the species IL-2.

The species listed above do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: The technical feature which links the species is that they are members of the genus of therapeutic proteins. Claim 1 is drawn broadly to an albumin fusion protein comprising therapeutic protein X. This invention does not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, it lacks a special technical feature because it fails to make a contribution over the prior art. For example, WO 93/15199 discloses therapeutic proteins, such as interleukins and interferons, fused to the albumin of SEQ ID NO:18 of the instant application. Because the invention as a whole fails to make a contribution over the prior art, the technical feature linking the claimed species cannot be a special technical feature under PCT Rule 13.2.